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ASSOCIATION OF FOUR SINGLE NUCLEOTIDE POLYMORPHISMS WITH ARTERIAL HYPERTENSION AND MYOCARDIAL INFARCTION IN THE RS (YA): ETHNIC AND GENDER FEATURES

ABSTRACT

The research of four single nucleotide polymorphisms (SNPs) association with arterial hypertension (AH) and myocardial infarction (MI) in population of the Republic of Sakha (Yakutia) depending on ethnicity and gender is carried out.

Keywords: single nucleotide polymorphisms, arterial hypertension, myocardial infarction, ethnicity gender and features, Republic of Sakha (Yakutia).

In Yakutia the cardiovascular diseases (CVD) in the structure of causes, both morbidity (19.1%) and mortality (47.4%), occupy a leading position [1]. Arterial hypertension (AH) is one of the main risk factors for the development of CVD and their complications, such as myocardial infarction (MI) and stroke. Currently in Russia, about 40% of the population (more than 42 million people) suffers from AH [2].

In recent years, a trend has been formed such as genetic cardiology, which integrates the concepts and technologies of molecular genetics for understanding the etiology and pathogenesis of CVD clinical polymorphism. The genetic approach allows creating a base for con-

ducting early diagnostics, selecting adequate treatment and prevention of CVD, which in the end will affect the quality of life of patients with cardiovascular pathology. One of the modern strategies for the search for genetic risk factors for the development of CVD is the full genome analysis of polymorphism of genes responsible for hereditary predisposition to them [5].

The aim of this study was to investigate the association of single nucleotide polymorphisms (SNRs) rs619203 gene ROS1 (6q22), rs4804611 gene ZNF627 (19p13.2), rs2549513 (16q23.1) and rs1376251 gene TAS2R50 (12p13.2) with arterial hypertension and myocardial infarction in population of the Republic of Sakha (Yakutia), taking into account ethnicity and gender.

MATERIALS AND METHODS

The research included 456 coronary heart disease (CHD) patients with the verified coronary atherosclerosis according to selective coronaroangiography (from them 396 men and 60 women) and 483 persons without clinical signs of CHD (from them 212 men and 271 women). Age of all surveyed participants made 45-64 years. Patients were recruited from National Centre of Medicine in Yakutsk (the main groups). Comparison groups were created by results of complex medical examination during departures to districts of the Republic of Sakha (Yakutia). Research period: 2007-2010. For the comparative analysis all examined persons were divided into 4 clinical groups: 1 – native patients with the verified coronary atherosclerosis (n=217), from them: men – 189, mean age 54,34 ± 0,44 yr and women – 28, mean age 53,39 ± 1,28 yr; 2 – non-native patients with the verified coronary atherosclerosis (n=239), from them: men – 207, mean age 54,76 ± 0,43 yr and women – 32, mean age 55,81 ± 1,01 yr; 3 – native persons without clinical signs of CHD (n=253), from them: men – 108, mean age 51,28 ± 0,57 yr and women – 145, mean age 51,19 ± 0,43 yr; 4 – non-native persons without clinical signs of CHD (n=230), from them: men – 104, mean age 51,09 ± 0,52 yr and women – 126, mean age 51,37 ± 0,47 yr. Yakuts are considered to be representatives of native nationality, non-native nationality – the Russians, Ukrainians and Belarussians living in Yakutia constantly.

Patients with coronary atherosclerosis were excluded if they had coronary arteries anomalies, intact coronary arteries, coronary artery bypass graft, existence of unstable angina, acute myocardial infarction in the anamnesis till 6 months. Criteria of exception for all groups: active inflammation, acquired and congenital heart diseases, cardiomyopathy, cancer and diagnosed of CHD for control groups, age are younger than 45 yr and more than 65 yr for all groups.

Genomic DNA was obtained from venous blood (10 ml) by phenol - chloroform extraction [4]. Genotyping was carried out by real-time PCR according to the protocol producer firms (probes TaqMan, Applied Biosystems, USA) on the ABI 7900HT (Applied Biosystems) according to the protocol producer firms. The following SNPs were included in this study: rs619203 gene ROS1 (6q22), rs4804611 gene ZNF627 (19p13.2), rs2549513 (16q23.1) and rs1376251 gene TAS2R50 (12p13.2). SNPs were selected by results of the Genome-Wide Association Studies which confirmed association of these SNPs with myocardial infarction. Genetic researches are conducted by staff of the Institute of Internal and Preventive Medicine. All researches are executed with the informed consent of examinees according to ethical standards of the Helsinki declaration (2000).

All data analyses were carried out with the statistical analysis software package SPSS 13.0 (SPSS Inc.). Any deviation of the genotype frequencies from the Hardy-Weinberg proportions was assessed by the χ2-test. The association between the SNPs and risk factors was estimated by criterion χ2-Pearson. Also used two-tailed the Fisher criterion for frequencies of genotypes and alleles. The association between SNPs and CHD risk was estimated by computing odds ratio (OR) and 95% confidence intervals (CI) from the multivariate logistic regression analyses. The probability level accepted for significance was $p < 0.05$.

RESULTS AND DISCUSSION

Genotypes frequencies in the natives and non-natives of Yakutia are presented in tables 1-2.

Rs619203 of ROS1 *gene (MIM 165020) (6q22)*. In non-native population the rs619203 was associated with AH (p=0.033) and MI (p=0.009). In women carrying the GG genotype was higher diagnosed the AH than carrying the genotype CC (p=0.002). In men carrying the CG genotype had higher frequency of MI than in men carrying the CC genotype (p=0.009). By results of the three-stage study (USA, 2005) the association of this SNP with IM [10] was revealed. However in the later works association of rs619203 with CHD and MI wasn't received [6, 7, and 11]. In the Russian study conducted in Novosibirsk the rs619203 was associated with anthropometric data and lipid levels [3].

Rs4804611 of *ZNF627 gene (*19r13.2*)*. The association of rs4804611 with AH in native women of the Republic of Sakha (Yakutia) was received. In native women carrying the AA genotype was higher frequency of AH in comparison with control group (77.6 vs 54.9% respectively, p=0.033). Association the rs4804611 with MI we not observed. Also no association of this SNP with MI in researches executed in the USA [6] and Germany [7] were observed. At the same time, in the earlier three-stage study (USA, 2005) the rs4804611 association with MI [10] was shown. This association was also confirmed in Japan [9]. In the Russian study association of rs4804611 with MI and

Table 1

Genotype frequencies of SNPs in patients with Arterial Hypertension (AH) and control group depending on ethnicity

SNPs	Genotype	Native				p	Non-native				p
		AH(+)		AH(-)			AH(+)		AH(-)		
		n	%	n	%		n	%	n	%	
rs619203 *ROS1*	CC	7	3,1	5	3,1		45	16	52	25,6	
	CG	56	24,5	44	27		120	42,7	75	36,9	0,033
	GG	166	72,5	114	69,9		116	41,3	76	37,4	
rs4804611 *ZNF627*	AA	170	72,6	116	70,3		158	56	119	58,3	
	AG	57	24,4	41	24,8		99	35,1	62	30,4	
	GG	7	3	8	4,8		25	8,9	23	11,3	
rs2549513 xp. 16	AA	205	88	154	93,9		210	75,3	161	78,2	
	AC	28	12	10	6,1		65	23,3	42	20,4	
	CC	0	0	0	0		4	1,4	3	1,5	
rs1376251 *TAS2R50*	CC	42	18,1	18	10,9		119	46,9	65	45,1	
	CT	94	40,5	88	53,3	0,023	101	39,8	56	38,9	
	TT	96	41,4	59	35,8		34	13,4	23	16	

Table 2

Genotype frequencies of SNPs in patients with Myocardial Infarction (MI) and control group depending on ethnicity

SNPs	Genotype	Native				p	Non-native				p
		MI(+)		MI(-)			MI(+)		MI(-)		
		n	%	n	%		n	%	n	%	
rs619203 *ROS1*	CC	5	4,3	7	2,5		9	7,4	87	24	
	CG	31	26,7	69	25		63	52,1	132	36,5	0,000
	GG	80	69	200	72,5		49	40,5	143	39,5	
rs4804611 *ZNF627*	AA	86	72,3	200	71,4		74	61,7	203	55,6	
	AG	31	26,1	67	24		38	31,7	122	33,4	
	GG	2	1,7	13	4,6		8	6,7	40	11	
rs2549513 xp. 16	AA	102	86,4	257	92,1		85	73,3	285	77,4	
	AC	16	13,6	22	7,9		25	21,6	82	22,3	0,001
	CC	0	0	0	0		6	5,2	1	0,3	
rs1376251 *TAS2R50*	CC	18	15,4	42	15		55	45,5	129	46,6	
	CT	39	33,3	143	51,1	0,002	46	38	111	40	
	TT	60	51,3	95	33,9		20	16,5	37	13,4	

levels of endogenic indicators was not revealed [3].

Rs2549513 *(*16q23.1*).* The association of rs2549513 with AH (p=0.028) in the natives and MI (p=0.001) in the non-natives we received. In native women carrying the AA genotype was high frequency of AH than women carrying the AC genotype (89.5 vs 10.5% respectively, p=0.028). Among non-native population in both gender groups and men carriers the AA genotype association with MI we received (all: 73.3 vs 21.6 vs 5.2%, p=0.001; men: 75.7 vs 20.4 vs 3.9%, p=0.041 respectively). In the Russian study (Novosibirsk) association of rs2549513 with MI was not revealed [3]. According to the Framingham study the rs2549513 was associated with CHD (MI and fatal CHD) [8].

Rs1376251 of *TAS2R50 gene (MIM 609627) (*12p13.2*).* Rs1376251 was associated with AH (p=0.023) and MI (p=0.002) among aboriginals of Yakutia. In both gender group and men carriers the CC genotype was higher frequency of AH in comparison with control group (all: 18.1 vs 10.9%, p=0.023; men: 18.8 vs 9.6%, p=0.004 respectively). At the same time MI was associated with TT genotype in comparison with control group (all: 51.3 vs 33.9%, p=0.002; men: 51.4 vs 32.4%, p=0.005 respectively). In the studies conducted in USA [6] and Germany [7] were no association between rs1376251 and MI. Though in the earlier three-stage study in USA association of this SNP with IM was shown [10]. In the Russian study in men with MI this SNP was associated with HDL level. In women with MI the rs1376251 was associated with index of waist circumference / hips circumference and TG level [3].

CONCLUSION

For the first time among population of the Republic of Sakha (Yakutia) the study of polymorphisms association rs619203 gene *ROS1* (6q22), rs4804611 gene *ZNF627* (19p13.2), rs2549513 (16q23.1) and rs1376251 gene *TAS2R50* (12p13.2) with arterial hypertension and myocardial infarction we conducted. According to our study was received the association of studied pathologies with different genetic markers in men and women of native and non-native population from Yakutia. The following associations with SNPs we received: with arterial hypertension – rs619203 of *ROS1* gene, rs4804611 of *ZNF627* gene, rs2549513 (16q23.1) and rs1376251 of *TAS2R50* gene; with myocardial infarction – rs619203 of *ROS1* gene, rs2549513 (16q23.1) and rs1376251 of *TAS2R50* gene. These genetic markers can be used for assessment of cardiovascular diseases development risk on the Russian (Yakutian) population.

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FREQUENCY OF M.1555A>G MUTATION IN *MT-RNR1* GENE OF MITOCHONDRIAL DNA AMONG DEAF INDIVIDUALS IN YAKUTIA

ABSTRACT

It has been established that the mutation m.1555A>G in the *MT-RNR1* gene in the homoplasmic state is associated with non-syndromic sensorineural hearing loss caused by the use of aminoglycoside antibiotics in many families of different ethnic origin. Earlier, the m.1555A>G mutation was detected on a small sample of patients (n = 65) in Yakutia with a frequency of 1.54%. In this study, we performed a search of the m.1555A>G mutation among additional sample of 108 hearing impaired individuals from Yakutia (Eastern Siberia, Russia). As a result, we found no mutation in this sample. When combining both samples (n=65 and n=108), the m.1555A>G mutation frequency in Yakutia is – 0.57% (1/173), and among the Yakut patients frequency of this mutation is 0.92% (1/108). The frequency of the m.1555A>G mutation among deaf patients in Yakutia is 0.57%, and is relatively low when compared with the global data.

Keywords: hearing loss, mitochondrial genome, m.1555A>G, *MT-RNR1*, Yakutia.

INTRODUCTION

It has been established that the mutation m.1555A>G in the *MT-RNR1* gene in the homoplasmic state is associated with non-syndromic sensorineural hearing loss caused by the use of aminoglycoside antibiotics in many families of different ethnic origin [3-5, 7, 8, 16]. The action of aminoglycosides is based on binding with the bacterial 16S rRNA of the small subunit of the ribosome, which results in the protein synthesis blocking. When adenine is replaced with guanine in *MT-RNR1* gene at 1555 bp position C-G pairing takes place in the human 12S rRNA site, which leads to a similarity to the A site of bacterial 16S rRNA, which is the target for aminoglycoside drugs [6] (fig. 1). Currently, most of the aminoglycoside drugs are used only for the treatment of severe infections, such as endocarditis, sepsis and tuberculosis [4]. However, in some developing countries, they are still being used as broad-spectrum drugs [9].

Earlier in Yakutia (Eastern Siberia, Russia) the m.1555A>G mutation was detected with a frequency of 1.54% in a small sample of patients (n = 65), 2.08% (n = 48) among Yakut patients, and the frequency of this mutation was 0.83% (n = 120) in the control sample of Yakuts without hearing impairment, [1]. The obtained values of the m.1555A>G mutation frequency indicated the urgency of conducting preventive diagnostics for the presence of this mutation before application of aminoglycoside antibiotics among the indigenous population of Yakutia. It is necessary to screen this mutation on larger sample of patients with hearing impairment to clarify the frequency of m.1555A>G in Yakutia.

Aim of study: To update data on frequency of the m.1555A>G mutation of the mitochondrial *MT-RNR1* gene in a sample of deaf patients in Yakutia in comparison with the world data.

MATERIALS AND METHODS

The sample of 108 hearing impaired individuals (66 female and 42 male) aged between 25 and 63 (mean age 44.7 ± 7.1 years) was selected. Ethnic composition of the sample: Yakuts - 60 patients; Russians - 20; individuals of other and mixed ethnicities - 28. Hearing impairment in the participants in the study was confirmed by an audiological study involving threshold tone audiometry using an audiometer "MAICO ST 20" (Germany) for air conduction at frequencies 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 kHz and bone conduction at frequencies 0.25, 0.5, 1.0, 4.0 kHz, step 5.0 DB. The degree of hearing loss was estimated at hearing thresholds of bet-

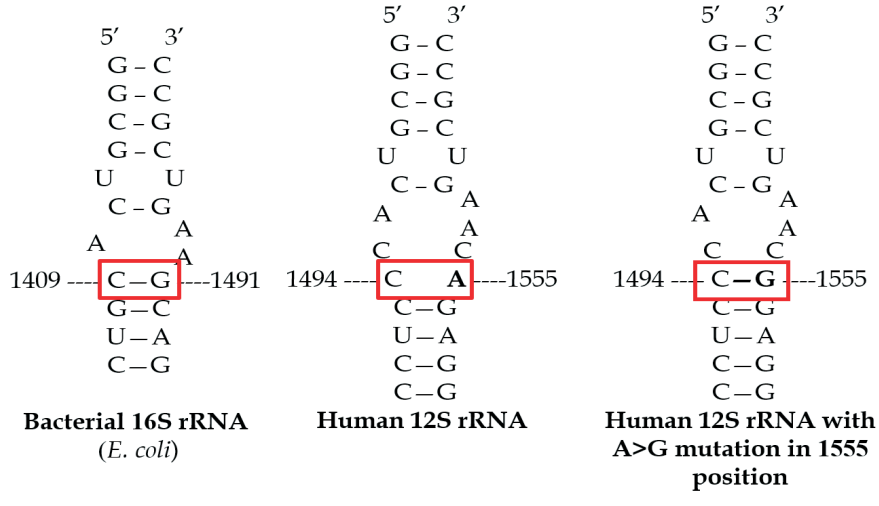

Figure 1. Molecular-genetic principle of aminoglycoside drugs action in case of m.1555A>G mutation. When adenine is replaced with guanine at the1555 bp position in the MT-RNR1 gene C-G pairing takes place in the human 12S rRNA site, which leads to a similarity to the A site of bacterial 16S rRNA, which is the target for aminoglycoside drugs [6].